

# Cerebral hyperperfusion syndrome after intracranial stenting: Case report and systematic review

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## Abstract

**Background:** Cerebral Hyperperfusion Syndrome (CHS) is an uncommon complication observed after intracranial angioplasty or stenting procedures. Given to the increasing use of new devices for intracranial angioplasty and stenting (INCS), in selected patients with high ischemic stroke risk, an equally increasing knowledge of complications related to these procedures is mandatory.

**Case description:** a 63-year-old man was diagnosed with an hyperperfusion syndrome after percutaneous angioplasty and stenting for severe symptomatic right internal carotid artery (ICA) siphon stenosis. After treatment he complained generalized seizures and respiratory failure. While conventional imaging did not demonstrate any acute brain lesions, Pseudo-Continuous Arterial Spin Labeling (PCASL) Perfusion MRI early documented right hemisphere blood flow increase suggestive for CHS.

**Conclusions:** Monitoring of perfusion changes after INCS could play an important a role in determining patients with high risk of CHS. ASL Perfusion MRI might be used for promptly, early diagnosis of CHS after treatment of severe intracranial artery stenosis.

## Keywords

Arterial Spin labeling, intracranial stenosis, intracranial angioplasty, intracranial stenting, cerebral hyperperfusion syndrome

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## Introduction

Cerebral Hyperperfusion Syndrome (CHS) is a rare but severe complication of revascularization procedures for chronic stenosis, probably due to a dysfunction of cerebral mechanism of autoregulation together with postoperative higher systemic blood pressure values (BP). CHS is a well known complication of carotid endarterectomy or stenting,<sup>1,2</sup> whereas has been poorly described after treatment of intracranial stenosis.

Intracranial angioplasty and stenting (INCS) is increasing due to the widespread diffusion of novel devices, therefore a greater knowledge of its complications is necessary.

## Clinical case

A 63-year-old smoker was admitted to our emergency department with left leg paresis, for about one-week. He did not reported any impairments of his daily activity (modified Rankin Scale 1), despite a right side

weakness presented some months before. Unenhanced CT scan showed a focal right frontal subacute ischemia (Figure 1(a)) and CT-Angiography documented tapering stenosis in the cervical segment and filling defect in the cavernous segment of both internal carotid arteries (ICAs); moreover the right hemispheric vasculature was poorly represented. Cerebral Digital Subtracted Angiography (DSA), showed severe stenosis of the right supraclinoid ICA, determining a reduction of blood flow for the middle cerebral artery (MCA) territories, and complete occlusion of left one. Thus, the vertebrobasilar system supplied the left hemisphere and the right anterior cerebral artery (ACA) territory through the left posterior

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communicating (PCoA) and the anterior communicating (ACoA) arteries. On the other hand, right MCA territories had neither primary nor leptomeningeal collateral supply (Figure 1). A conventional 3-Tesla MR, with Pseudo-Continuous Arterial Spin Labeling (PCASL) sequence, confirmed the subacute ischemic lesion and documented reduction of the cerebral blood flow (CBF) in the right hemisphere (Figure 2(d)).

MR study was performed with MAGNETOM Skyra 3T (Siemens Healthcare, Erlangen, Germany); protocol included a 3D PCASL sequence, using a labeling period of 700 ms, followed by a 1290 ms post-label delay (inversion time 1990 ms). Whole-brain images were obtained with a 3D background-suppressed Gradient and Spin-Echo (GRASE) sequence, with a TR of 5 s, turbo factor = 18 and EPI the sequence factor = 21. The sequence required a 4:05-minute acquisition time. Other ASL parameters were: TE 16.38 ms; FOV 192 × 192 mm; matrix 64 × 64; measurements 2, and averages 1, Bandwidth 2604 Hz/Px.

Patient was premedicated with dual antiplatelet therapy (Acetylsalicylic acid 100 mg and Clopidogrel 75 mg) and hypolipemic therapy (Statin 40 mg), and scheduled for the endovascular treatment. After one week, INCS of the intracranial right ICA stenosis

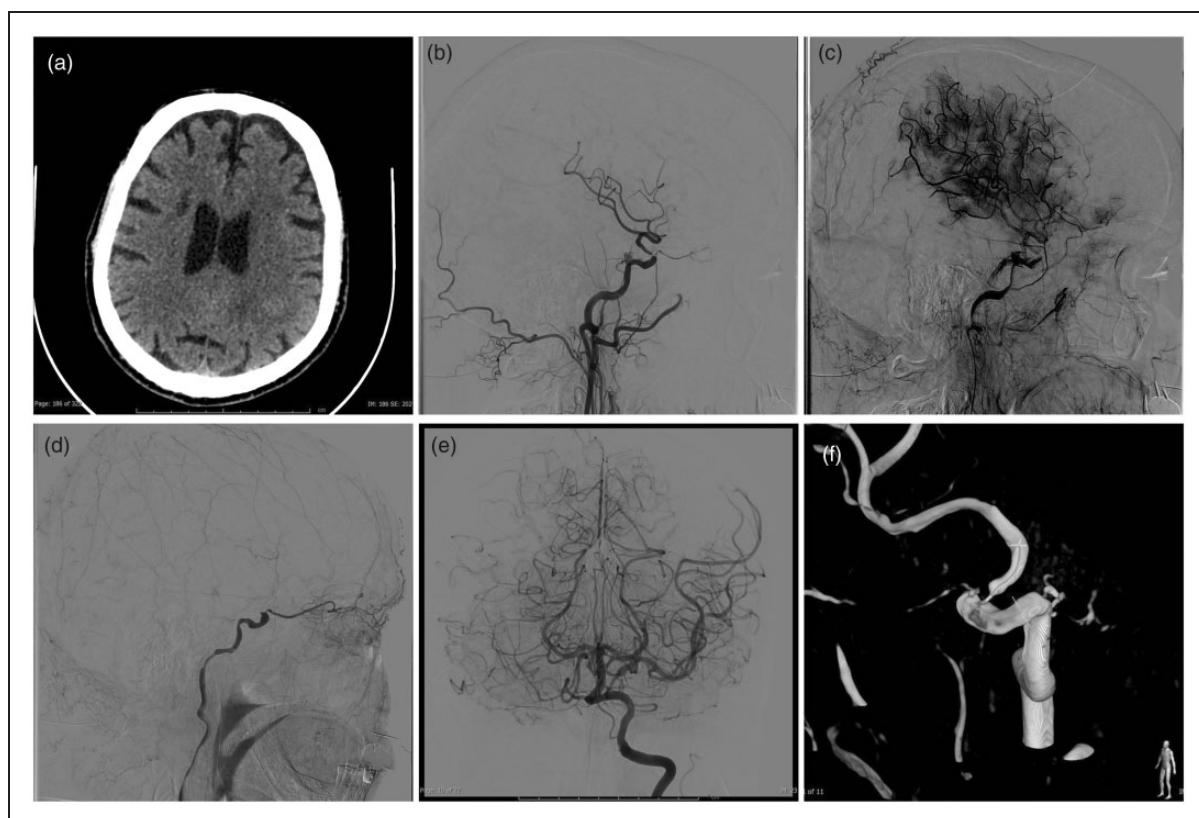
(Neurospeed 2.5 × 8 mm and Credo 4 × 15 mm, Acandis GmbH, Pforzheim, Germany) was performed under general anesthesia, resulting in significant dilatation of the ICA stenosis and increased blood flow for the right MCA territories.

After treatment, the patient developed seizures and respiratory failure, necessitating anaesthesiologic intervention.

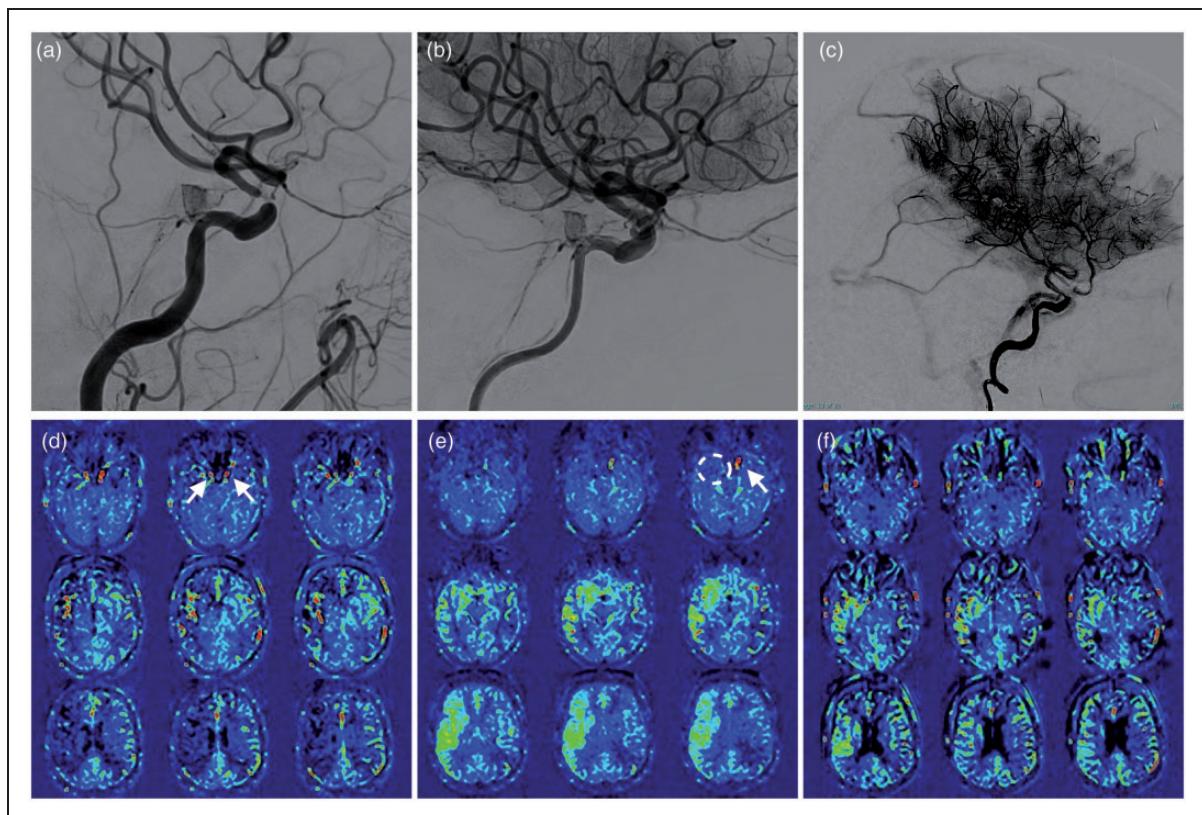
Unenhanced CT and MR controls did not demonstrate procedural complications. PCASL showed raised CBF values in the right hemisphere, suggesting a CHS (Figure 2(e)). This condition was managed with strict control of blood pressure (systolic BP < 150 mmHg) and intravenous mannitol.

After treatment, the patient presented fluctuating cognitive impairment and right arm paresis for two days, that progressively improved. Electroencephalography obtained during this period revealed epileptiform discharges on the right side. Another MR examination performed five days after treatment did not show focal ischemic lesions, while the PCASL study documented a slight reduction of the right hemispheric hyper-perfusion (Figure 2(f)).

In the following days the patient did not present newer focal neurological deficits and was discharged with mRS 1 after 10 days.



**Figure 1.** (a) unenhanced CT scan showing focal subacute ischemic lesions of the right white matter. (b/c) right internal carotid artery injection showing severe stenosis of the right supraclinoid segment, with slow and poor blood flow for the middle cerebral artery territories. (d) left internal carotid artery injection showing a supraclinoid occlusion. (e) left vertebral artery injection showing collateral circulation from the left posterior communicating artery for the left brain hemisphere and the right anterior cerebral artery territories. (f) 3D acquisition of the right internal carotid artery.



**Figure 2.** (a) pre-treatment right internal carotid artery; (b/c) post-treatment right internal carotid artery with stenosis dilatation and a better visualization of the arterial tree, a prominent capillary blush and early draining veins of the treated territories. (d) CBF map of pre-treatment PCASL showing hypoperfused right middle cerebral artery territories and the “slow flow sign” in both cavernous carotid arteries (white arrow); (e) CBF map of post-treatment PCASL showing hyperperfused right middle cerebral artery territories and the disappearance of the slow flow sign in treated internal carotid siphon (white circle). (f) 2 days after treatment CBF map of PCASL showing reduction of the hemispheric hyperperfusion.

## Discussion

CHS is an uncommon complication of revascularization procedures for chronic stenosis, determining variable clinical manifestations, from mild symptoms, such as headache, to severe presentation.<sup>3</sup> CHS has been described after carotid endarterectomy or angioplasty and stenting, with a frequency range from 1.1 to 6.8% and a mortality range from 3 to 26%, following intracerebral hemorrhage (ICH).<sup>2,4,5</sup> Otherwise, the occurrence of this complication after INCS is much less known, with only few cases described. The results of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial<sup>6</sup> might have limited the use of INCS, despite some promising studies have been published recently.<sup>7,8</sup>

We reviewed the medical literature about CHS after treatment of intracranial artery stenosis searching on Pubmed and combining search terms for “hyperperfusion syndrome” and “intracranial stenosis”. All studies reporting HS after treatment of intracranial stenosis have been listed in Table 1. Evaluation was performed according to the

“Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) statement, including methods of publication search, eligibility, data collection, extraction, analysis, and preparation of the systematic review report (Figure 3). Articles reporting CHS related to cervical ICA stenosis have been excluded.

CHS has been reported in 12 cases report(2) (Table 1). Nine patients had MCA stenosis, five had vertebral stenosis, four had intracranial internal carotid artery stenosis and one had basilar artery stenosis. Our case displayed focal neurological deficits to right MCA hypoperfusion; interestingly, it was a right ICA stenosis acting like an MCA stenosis, since the right ACA territory was not hypo-perfused as demonstrated by the PCASL.

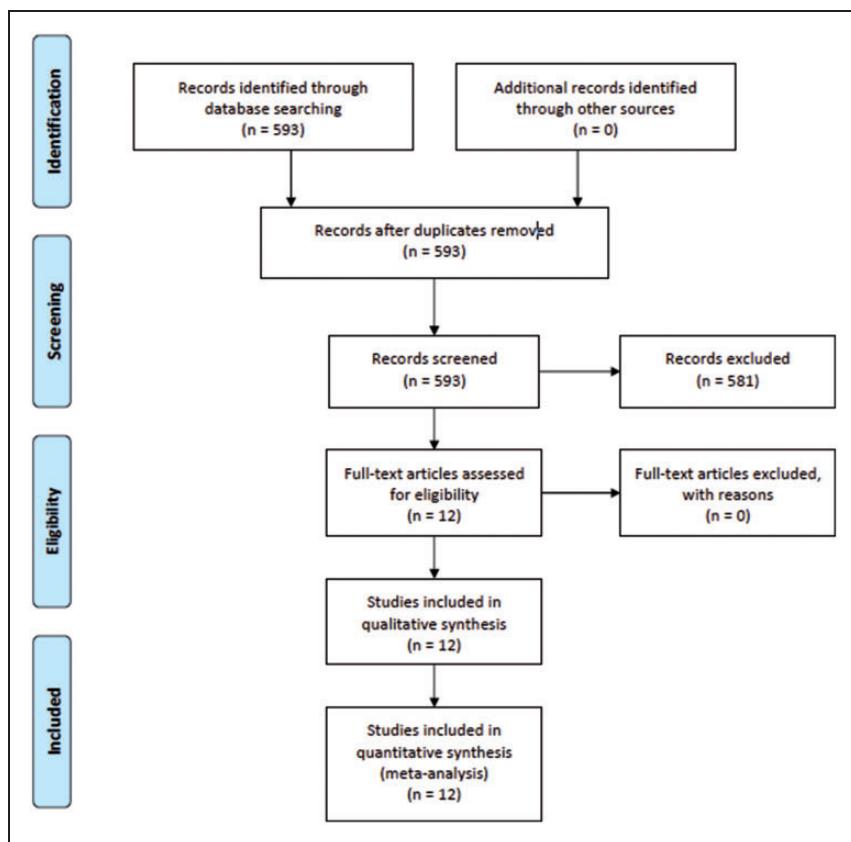
Seventeen patients developed a ICH, all of them taking antiplatelet or anticoagulation therapy. There are no published data about the effect of medication protocol used for intracranial stenting on the haemorrhagic rate in such patients; we can only suppose that it may lead to a higher rate of haemorrhagic events.

Sixteen patients were treated with stent, 2 with PTA and 3 with PTA and stent. Due to the small

**Table 1.** Medical literature about CHS after intracranial stenosis treatment.

References	No. of patients	Stenosis location	Treatment technique	Anticoagulation/antiaggregation	Neurological symptoms	Diagnosis of CHS	Hemorrhage
Meyers et al. <sup>3</sup>	1	Bilateral VA	Stenting	DAPT	Headache, altered sensorium, focal neurological deficit and hypertension	Clinical CT scan	No
Bando et al. <sup>4</sup>	1	VA	PTA	Heparine	No	SPECT scan	No
Liu et al. <sup>5</sup>	1	MCA	PTA	Heparine	Right hemiparesis and aphasia	CT scan showing ICH	Yes
Qureshi et al. <sup>6</sup>	3	1 ICA / 2 MCA	Stenting	DAPT	Neurological deterioration	CT scan showing ICH	Yes
García-Bargo et al. <sup>7</sup>	1	ICA	Stenting	DAPT	Neurological deterioration	CT scan showing ICH	Yes
Rezende et al. <sup>8</sup>	1	VA	Stenting	Clopidogrel	Agitation followed by apathetic state	CT scan showing ICH	Yes
Terata et al. <sup>9</sup>	2	ICA / VA	PTA / Stenting	DAPT	Neurological deterioration	CT scan showing ICH SPECT scan	Yes
Jiang et al. <sup>10</sup>	1	VA	Stenting	DAPT	Neurological deterioration	CT scan showing ICH	Yes
Zhang et al. <sup>11</sup>	1	VA	Stenting	DAPT	Headache and vomiting	CT scan showing ICH	Yes
Wolfe et al. <sup>12</sup>	1	MCA	Stenting	DAPT	Focal neurological deficit	CT scan showing focal oedema	No
Xu et al. <sup>13</sup>	6	5 MCA / 1 BA	Stenting	DAPT	Neurological deterioration	CT scan showing ICH	Yes
Mondel et al. <sup>12</sup>	1	ICA	Stenting	DAPT	Neurological deterioration	CT scan showing ICH	Yes
Our case	1	ICA	PTA / Stenting	DAPT	Altered sensorium and fluctuating right arm paresis	MR perfusion with PCASL	No

BA: basilar artery; DAPT: doble antiplatelet therapy; ICA: internal carotid artery; MCA: middle cerebral artery; PTA: percutaneous angioplasty; VA: vertebral artery .

**Figure 3.** PRISMA flow-chart.

number of patients it is not possible to evaluate the relation between type of treatment and CHS rate. However, according to literature about extracranial ICA stenosis, staged angioplasty might be a strategy to allow gradual adaptation of brain to increased

CBF values.<sup>9</sup> Further studies applying this strategy to ICAs could clarify this hypothesis.

Our case and all reported ones had a preoperative stenosis degree higher than 60%. Data about collateral status were unclear. According to the

Thrombolysis in Cerebral Infarction (TICI) score and the American Society of Intervention and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) score, our patient had an antegrade flow across stenosis with partial perfusion of the entire vascular bed (TICI 2A) and leptomeningeal collateral flow limited to the periphery of the ischemic site (score 1). Both factors, stenosis degree and collateral circulation might be predictors of CHS. High grade stenosis is always a sign of hemodynamic compromise, while the collateral circulation play a different role depending on stenosis location with respect to the circle of Willis: in proximal stenoses, an incomplete setting of the circle represent a higher risk of CHS,<sup>10</sup> whereas in distal ones (isolated MCA stenoses) a good leptomeningeal collateral status is another sign of hemodynamic compromise and hence a predictor of CHS.<sup>11</sup>

After treatment there is an overload of blood flow in distal territories and some angiographic findings related to this phenomenon might suggest disruption of cerebral autoregulation,<sup>12</sup> as in our case: increased diameter of arterial branches, prominent capillary blush and early draining veins of the treated territories. These flow alterations can be also monitored with intraoperative near-infrared spectroscopy (NIRS)<sup>13</sup> or MCA mean flow velocities (Vm) measured by transcranial Doppler (TCD).<sup>14</sup> In our opinion, the association between angiographic findings and intraoperative monitoring with NIRS<sup>15</sup> or MCA Vm measured by TCD<sup>13</sup> might play a role in identifying patients at risk of CHS.

In reported cases, CHS was mostly a clinical diagnoses. Fifteen patients developed neurological deficits secondary to ICH or brain oedema, and none of them was studied with perfusion imaging. Only two papers examined perfusion alterations,<sup>16,17</sup> through single photon emission computed tomography (SPECT) imaging. Among these three patients, just one of them was asymptomatic without brain damage on CT scan. These data led to different speculations: they might suggest that perfusion alterations are rare in asymptomatic patients, or alternatively underestimated and more frequent than we think. Our hypothesis might find an explanation in the pathophysiology of the CHS. Actually, cerebral hyperperfusion is a foreseeable phenomenon caused by the sudden restoration of distal flow, which represents the goal of ICAs angioplasty and stenting; conversely, CHS is a disease caused by the impairment of cerebral autoregulation, secondary to myogenic and neurogenic processes that involve brain arterioles in patients with extracranial or intracranial stenosis.<sup>18</sup> These processes are essential for the development of collateral circulation, but they reduce the Cerebral VasoReactivity (CVR).<sup>19</sup> Thus according to this idea, the hyper-perfusion represents a trigger factor of the CHS; it might be autoregulated in asymptomatic patients with a preserved CVR or might be cause

of a syndrome with vast spectrum of symptoms and radiological presentation in patients with reduced CVR. An immediate post-procedure CBF study, as in our case, may show the CH induced by treatment early. Obviously larger studies are needed to deeply evaluate the predictive value of perfusion studies in diagnosing CHS.

To our knowledge there are only few studies dealing with perfusion alterations in CHS, all of them after extracranial carotid stenting. These studies showed that quantitative and qualitative CBF imaging techniques, such as SPECT, CT and MR Perfusion-Weighted Imaging (PWI) and Arterial Spin Labeling (ASL) might identify patients at risk for CHS.<sup>14,20-23</sup>

This is the first case of post-stenting CHS documented with the PCASL. ASL is a completely non-invasive technique of brain MRI perfusion, in which magnetically labelled blood rather than contrast agent is used as a tracer. ASL combines features of both angiography and perfusion, since its ability to quantify CBF is closely related to the Arterial Transit Time (ATT). In fact, in steno-occlusive disease, CBF could be underestimated in regions with delayed ATT. However, it has been demonstrated that ASL with multiple Post-Labeling Delays may solve this problem and may be a useful screening tool to predict postoperative CHS after CEA.<sup>21</sup> On the other side this drawback may be turned to advantage for visualizing collaterals, since hypoperfused territories are characterised by longer arterial arrival time. This late-arriving flow appears as serpiginous high signal within cortical vessels, which has been defined Arterial Transit Artifact (ATA).<sup>15,24,25</sup> The ATA has been used to quantify collateral circulation in patients with cerebrovascular diseases, such as intracranial arterial stenosis or Moya-Moya disease.<sup>26</sup> In our case we noticed the ATA within cavernous segment of both ICAs, proximal to the occluded and stenotic tracts; in the first PCASL, the pre-stenotic portion of the right ICA showed the ATA (Figure 2 (d)) which disappeared in PCASL post-treatment (Figure 2(e) and (f)). So far this “slow flow sign” has never been documented and, in our opinion, it might represent an useful marker for detect intracranial stenosis.

ASL imaging has been compared with bolus PWI, showing potential advantages: a shorter reconstruction time, no needs of motion correction, the ability to identify bilateral disease and to detect more subtle perfusion alterations.<sup>27</sup> A shorter acquisition time has been also reported, but this is not true for ASL sequences with multiple PLD, requiring around 10 minutes to obtain perfusion images.<sup>21</sup>

## Conclusion

CHS is a potentially severe and underestimated complication of intracranial artery stenosis.

Intraoperative monitoring of CBF and angiographic changes after treatment could play a role in determining patients with high risk of CHS. ASL imaging before and after intervention might be used to assess hemodynamic alterations in brain perfusion in order to predict and to diagnose the CHS. Further studies about the use of PCASL in cerebro-vascular stenotic diseases are necessary.

### Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### Informed consent

Informed consent was obtained from all individual participants included in the study.

### Declaration of conflicting interests

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